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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,375	09/29/2005	Ragab El-Rashidy	GENIX-103	3124

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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
08/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/551,375	EL-RASHIDY, RAGAB	
	Examiner	**Art Unit**	
	MARCELA M. CORDERO GARCIA	1654	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 30 June 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-23 and 26*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

Continuation of 3. NOTE: Applicant argues that neither Garnick et al. nor Lu et al teach the administration of leuprolide together with calcitriol. Neither does Beer ae al. This secondary reference only describes the co-administration of calcitriol and docetaxel, paclitaxel and platinum compounds. Beer et al. contains no suggestion whatsoever that leuprolide, an LHRH agonist, or any other LHRH agonist analog should or could be substituted for docetaxel, paclitaxel or platinum compound. There must be some teaching in the prior art that supports the combination (DCS Hosp. Sys., Inc. V. Montefiore Hosp., 4732 F.2d 1572, 1577; 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). Here there is none. Additionally, no predictability has been shown as to the effect of calcitriol when combined with an LHRH-R agonist. The teachings of Garnick et al. have been mischaracterized as well. To treat prostate cancer, Garnick et al. teaches the administration of LHRH-R antagonist prior to surgery.. Leuprolide is not a LHRH-R antagonist, rather a LHRH-R agonsit which is administered only after the tratment with a LHR-R antagonist (Garnick et al., Examples 2 and 3). Nothin in Garnick et al. would have led one of ordinary skill, whatever that skill level may have been, to (1) ignore the epxress teachings of Garnick et al. vis-à-vis the use of LHRH-R antagonist and instead (2) administer calcitriol together with leuprolide, a LHRH-R agonist. Also, nothing in Garnick et al. would have led one of ordinary skill in the art to the Beer et al. reference. Furthermore, it is well established that the asserted interpretation of prior art cannot be inoperable. In re Gordon, 733 F.2d 900, 902; 221 USPQ 1175, (Fed. Cir. 1984). The conclusion is inescapable that the attempted combination of Garnick et al. and Beer et al. has been arrived at only by an impermissible hidsight reconstruction of the claimed invention using applicant's own teachings as a guide. One of ordinary skill would not have attempted the combination of these particular references based on the teachings thereof. There are no teachings in Beer et al. that would have led one of ordinary skill to Garnick et al. The Examine'rs contention that the present claims do not exclude the use of LHRH-R antagonists is not well taken. One of ordinary skill, whatever that skill level may be, would not have had any reason whatsoever to co-administer an agonist together with an antagonist. No rationale has been advanced by the Examiner why one of ordinary skill would have done so. Besides, one cannot use hindsight reconstruction to pick and choose among isolated prior art disclosures to vititate the claimed invention. In re Fine, 837 F.2d 1071, 1075, 5 USPQ 2d 1596 1600 (Fed. Cir. 11988). Lu et al. does not cure the defects of Garnick et al. or Beer et al. as references against the present claims. The amino acid residue sequence of Leuprolide is not an issue here. The Examiner agrees. Further, as also recognized by the Examiner, the express limitations of claims 17, 19, 21, 22 and 23 are not taught by Granick et al. The level of ordinary skill in the pretinent art has not been resolved in this case, thus on the presetn record it cannot be determined what limitations would or would not have been obvious to noe of ordinary skill. A mere statement by the Examiner that the level of ordinary skill is set forth by the references provided is of no moment, and does not support the finidngs of fact madated by Graham v. john Deere, 383 US 1, 17, 148 USPQ 459 (1966). The onus is on the Examiner to make out a prima facie case of obviousness for the claimed invention. The Examiner has failed to do so. The rejection based on 35 USC 103 (a) is not supportable, and should be withdrawn. The continued rejection of claims 1, 5-15 and 26 under 35 USC 103(a) as unpatentable over Garnick et al. in view of Beer et al., conway et al. and Chen likewise is unwarranted, and is traversed as well. Garnick et al. and Beer et al. fail as references against claims 1, 5-15 and 26 for the same reasons as those advanced hereinabove. Additionally, as recognized by the Examiner, the express limitation of 1 to about 30 micrograms of calcitriol with a polysorbitan as called for in claims 6, 7, 12 and 26 is not taught. Likewise, the expresss limitaion of 5 to about 30 micrograms of calcitriol with a polysorbitan as called for in claims 12 and 13 is not taught. The Examiner's assertion that "obvious to try" is an appropriate test of obviousness in this case is not supported by the record. The contation that "there where limited number of methodologies available to do so, such as those of Beer et al. and Garnick et al. is not supported by the record. The examiner has adduced no evidence that the Garnick et al. and Beer et al. methodlogies indeed were the only methodologies available to one of ordinary skill in the art. Beer et al. discuss the treatment of androgen-indepented prostate cancer using calcitriol to enhance the activity of docetaxel, paclitaxel, and platinum compounds, not the LHRH-R antagonists of Garnick et al. described in Table I. Also in col. 1, lines 11-63 of Garnick et al., a wide variety of prostate cancer treatments is described in addition to those described as the purported invention. For suitable LHRH-R antagonists, see Garnick et al., col. 3, line 55 at seq. Table I alone lists 134 LHRH-R agonist in combination with calcitriol. Neither does Beer et al. Neither Conway et al. nor Chen cure the foregoing defects of Garnick et al. and Beer et al. Conway et al. is clearly inapposite, because it is directed to the treatment of neonatal hypocalcemia with an aqueous calcitriol solution. This has nothing to do with the presently claimed method for treating advance prostate cancer. Chen is also inapposite vis-à-vis the present claims. Chen teaches solubilizers for paclitaxel (col. 7, line 8) and possibly leuprolide(col. 7, line 23). These solubilizerr are PEG-Vitamin Es, quaternary ammonium salts, PEG-monoacid fatty esters, PEG-glyceryl fatty esters, polysorbates PEG-fatty alcohols (col. 7, lines 13-18; col. 14, line 67 to col. 15, line 3). Calcitriol clearly is not encompassed by the foregoing teaching, nor is calcitriol mentioned as an osteoporosis agent at col. 7, line 59, that can be solubilized using a paclitaxel solubilizer. By no stretch of the imagination does Chen teach a combination of leuprolide with calcitriol or a combination of leuprolide, calcitriol and polysorbate 20, much less the presently claimed method. Applicant's arguments above have been carefully considered by Examiner, but not deemed persuasive for the reasons of record and for the following reasons: (1) The instant claims are drawn to a method of treating advanced prostate cancer comprising leuprolide (or an LHRH agonist) and calcitriol in an amount sufficient to enhance the effectiveness of the LHRH agonist analog. The instant claims, as drafted, do not exclude (see transitional phrase: "comprising of") other compounds from being administered along with the leuprolide and calcitriol. (2) Examiner has arrived to the conclusion that both leuprolide and calcitriol can be used in a method for treating advanced prostate cancer, since either one individually can be used in treating advanced prostate cancer. Therefore, there is no impermisible hindsight reconstruction. The references are linked by the use in treating advanced prostate cancer. (3) With respect to the statement that "The Examiner's contention that the present claims do not exclude the use of LHRH-R antagonists is not well taken", Examiner re-states that the instantly claimed method "comprises of" administration of LHRH agonist and calcitriol, which does not exclude additional method steps. With regards to the statements that "One of ordinary skill, whatever that skill level may be, would not have had any reason whatsoever to co-administer an agonist together with an antagonist." and that "No rationale has been advanced by the Examiner whiy one of ordinary skill would have done so." Examiner re-states that the methods of Garnick et al. and Beer et al. are both directed to treating advanced prostate cancer, and "It has been held that combinations of two or more compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is to be used for the very same purpose. In re Susi, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971). Therefore "combining them flows logically from their having been individually taught in prior art" as explained in In re Crockett, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (1960). (See Office action dated 31 March 2008, page 4, last paragraph). (4) With regards to the claimed dosages, the rejection stands for the reasons of record. (5) With regards to the statement that "The examiner has adduced no evidence that the Garnick et al. and Beer et al. methodologies indeed were the only methodologies available to one of ordinary skill in the art", Examiner respectfully clarifies that nowhere in the record the statement has been made that these were the only methodologies available, but rather that there were a limited number of methodologies available for the treatment of advance prostate cancer (see, Office Action dated 31 March 2008, page 11, second paragraph). (5) The remarks with respect to Conway et al. and Chen et al. are not deemed persuasive for the reasons of record and because the references are relied upon

to show art accepted ways of administration and suitable excipients/adjuvants within compositions containing leuprolide or calcitriol. Therefore the 103(a) rejections of record are maintained.